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Hemodynamics and functional state of the contralateral kidney in the early postoperative period after surgical treatment of kidney cancer

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AIM: To study the hemodynamics and functional state of the renal tissue of the contralateral kidney in the early postoperative period after surgical treatment of kidney cancer.

MATERIALS AND METHODS: The prospective study included 58 patients with renal cell carcinoma, 36 (62.1%) of whom underwent radical nephrectomy, and 22 (37.9%) underwent partial nephrectomy. Tumor sizes ranged from 1.0 to 12.0 cm. All patients before surgery and in the early postoperative period underwent ultrasound examination of the structure and size of the kidneys, Doppler ultrasonography of the renal vessels, biomicroscopy of the bulbar conjunctiva, measured peripheral blood pressure, determined the glomerular filtration rate (GFR) and performed a coagulogram. The control group included 16 healthy adults.

RESULTS: In 83.3% of patients after radical nephrectomy and in 13.6% of patients after partial nephrectomy a tendency towards an increase in blood pressure compared with the initial values was noted by the 2-4th day after the operation. By the 5th day after surgery, the volume of the only kidney remaining after radical nephrectomy increased by an average of 4% (from 126.1 ± 1.4 to 131.2 ± 2.1 cm^3, $p < 0.05$), while after partial nephrectomy has not changed reliably. After surgery, a decrease in GFR was detected in 34 (58.6%; $p < 0.05$) patients, including after radical nephrectomy ($n = 28$) – up to 73.4 ± 8.2 ml / min / 1.73 m^2, after partial nephrectomy ($n = 6$) – up to 98.2 ± 3.4 ml / min / 1.73 m^2. Doppler ultrasonography of the vessels of a single kidney in patients after radical nephrectomy showed a moderate increase in linear blood flow, an increase in the resistance index in the main trunk of the renal artery, and a decrease in the pulsation index in the segmental and arc arteries. In patients after partial nephrectomy in the contralateral kidney these changes were not observed. When performing biomicroscopy of the bulbar conjunctiva in 83.3% of patients after radical nephrectomy and in 13.6% of patients after partial nephrectomy, changes in the microvasculature were revealed: narrowing of arterioles, expansion of venules, slowing of venular and capillary blood flow. Before the operation and in the early postoperative period, the content of fibrinogen and soluble fibrin-monomer complex in the blood of patients with renal cell carcinoma was significantly higher than in the control group.

CONCLUSIONS: In patients with renal cell carcinoma, changes in the contralateral kidney in the early postoperative period after radical nephrectomy are significantly more pronounced than after partial nephrectomy, and are accompanied by changes in systemic and local hemodynamics and kidney function. The results of the study confirm the feasibility of performing organ-preserving surgeries in patients with renal cell carcinoma.

Keywords: renal cell carcinoma; radical nephrectomy; partial nephrectomy; kidney microcirculation.

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Гемодинамика и функциональное состояние контралатеральной почки в раннем послеоперационном периоде после хирургического лечения рака почки

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Цель — изучить гемодинамику и функциональное состояние почечной ткани контралатеральной почки в раннем послеоперационном периоде после хирургического лечения рака почки.

Материалы и методы. В проспективное исследование вошли 58 больных почечно-клеточным раком, 36 (62,1 %) из которых была выполнена нефрэктомия, а 22 (37,9 %) — резекция почки. Размеры опухоли находились в пределах от 1,0 до 12,0 см. Всем больным до операции и в раннем послеоперационном периоде выполняли ультразвуковое исследование структуры и размеров почек, доплерографию сосудов почек, биомикроскопию бульбарной конъюнктивы, измеряли периферическое артериальное давление, определяли скорость клубочковой фильтрации и выполняли коагулограмму. В контрольную группу включены 16 здоровых взрослых.

Результаты. У 83,3 % пациентов после нефрэктомии и 13,6 % после резекции почки ко 2–4-м суткам после операции отмечена тенденция к повышению артериального давления по сравнению с исходными значениями. К пятым суткам после операции объем единственной оставшейся после нефрэктомии почки увеличился в среднем на 4 % (с 126,1 ± 1,4 до 131,2 ± 2,1 см^3, $p < 0,05$), тогда как после резекции достоверно не изменился. После операции снижение скорости клубочковой фильтрации выявлено у 34 (58,6 %, $p < 0,05$) пациентов, из них после нефрэктомии ($n = 28$) — до 73,4 ± 8,2 мл/(мин·1,73 м^2), после резекции почки ($n = 6$) — до 98,2 ± 3,4 мл/(мин·1,73 м^2). При доплерографии сосудов единственной почки у пациентов после нефрэктомии отмечали умеренное повышение линейного кровотока, повышение индекса резистентности в основном стволе почечной артерии, снижение пульсационного индекса в сегментарных и дуговых артериях. У пациентов после резекции в контралатеральной почке указанных изменений не отмечено. При биомикроскопии бульбарной коньюнктивы у 83,3 % больных после нефрэктомии и у 13,6 % после резекции почки выявлены изменения в микроциркуляторном русле — сужение артериол, расширение венул, замедление венулярного и капиллярного кровотока. До операции и в раннем послеоперационном периоде содержание фибриногена и растворимого фибрин-мономерного комплекса в крови больных почечно-клеточным раком было достоверно выше, чем в контрольной группе.

Выводы. У больных почечно-клеточным раком изменения контралатеральной почки в раннем послеоперационном периоде после нефрэктомии существенно более выражены, чем после резекции, и сопровождаются изменением системной и локальной гемодинамики и функции почки. Результаты исследования подтверждают целесообразность выполнения органосохраняющих операций больным почечно-клеточным раком.

Ключевые слова: почечно-клеточный рак; радикальная нефрэктомия; резекция почки; микроциркуляция почки.

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ЭКО•ВЕКТОР

INTRODUCTION

Renal cell carcinoma (RCC) poses a significant medical and social burden, ranking first in terms of incidence and ninth in terms of morbidity among all malignant neoplasms [1–3]. It consists of 4.3% of all cancers in men and 2.9% in women [3–5]. In Russia, more than 23,000 new cases of renal cancer are detected annually, including 47.9% of stage I, 16% of stage II, 15.5% of stage III, and 19.1% of case of stage IV, respectively [1, 2].

Contemporary trends in surgical oncourology consist in the development of organ-preserving guidelines, which became possible due to an increase in the efficiency in diagnosing early malignant tumors and initiating timely treatment [6–9]. Nevertheless, the frequency of radical nephrectomy (RNE) in RCC remains high, and the number of patients with a solitary kidney is on a steady rise [5]. The results of numerous experimental studies and clinical cases indicate that the remaining conditionally "healthy" kidney is highly susceptible to various diseases progressing often to chronic kidney disease [10–13]. It has been proven that the removal of the kidney itself is a significant factor in the development of chronic kidney disease, leading to increased probability of metabolic complications, vascular diseases, and lethal outcomes [10, 13]. At the same time, a number of issues related to the state of the contralateral kidney after surgery for RCC are unclear.

We therefore aimed at analyzing the condition of the contralateral kidney in the early postoperative period after surgical treatment of RCC.

MATERIALS AND METHODS

From 2014 to 2018, 615 patients with diagnosed kidney cancer were operated upon in the urology and oncourology departments of the City Clinical Hospital No. 1. We included 58 patients in this prospective open-label comparative non-interventional study. All patients were divided into two groups depending on the type of surgery. Group 1 included 36 patients who underwent RNE, including 23 men and 13 women, with an average age of 52.6 ± 2.41 years. Group 2 consisted of 22 patients after resection of the kidney tumor within the healthy tissue, including 16 men and 12 women, with an average age of 48.7 ± 2.6 years. The size of the kidney tumor ranged from 1.0 to 12.0 cm. We excluded those with a history of arterial hypertension, electrocardiographic changes characteristic of hypertension, as well as those with signs of heart failure. The control group included 16 healthy blood donors, namely 10 men and 6 women aged 46 to 54 years.

Before surgery and in the early postoperative period, all patients underwent renal ultrasounds with the calculation of the kidney volume according to the formula $V = A \times B \times C \times 0.53$, where A is the length, B is the width, C is the thickness of the kidney, as well as renal doppler ultrasound with the determination of linear blood flow, resistance index and pulsation index, biomicroscopy of the bulbar conjunctiva, and peripheral blood pressure (mean dynamic pressure was calculated by the formula $P_c = P_d + P_n$, where P_d – diastolic pressure, P_n – pulse pressure); glomerular filtration rate (GFR) was determined, and a coagulogram was performed.

The study of the bulbar conjunctiva was performed using a special portable device consisting of a support, an MBS2 microscope, and an illumination device (electronic pulse lamp). A ×7 objective and a ×10 eyepiece were used, which gives a magnification by 65 times; at a higher magnification, focusing on an object is difficult. Duplex scanning was performed on a SonoScape S20 apparatus using a convex multifrequency transducer.

The degree of complexity of the planned kidney resection was determined using the R.E.N.A.L. nephrometric scoring system (R. – maximum diameter in centimeters, E. – exophytic/endophytic growth, N. – distance from the tumor to the renal cavity system in millimeters, A. – anterior/posterior location of the tumor, L. – location of the tumor relative to the pole lines) according to the results of computed tomography or magnetic resonance imaging of the retroperitoneal organs, which averaged 7.4 ± 0.8 points in group 2 patients.

All patients underwent comprehensive prophylaxis of thromboembolic complications, including elastic compression of the lower extremities, early physical rehabilitation of patients, and administration of low-molecular-weight heparins in prophylactic doses.

The study was performed in accordance with the principles of the Declaration of Helsinki. Data was analyzed using the Statistica statistical software package and the level of significance was set at 0.05 (p-values less than 0.05 were considered statistically significant).

RESULTS AND DISCUSSION

Among all patients included in the study, there were no III–V degree complications in the postoperative period, according to the Clavien–Dindo classification. The duration of stay in the intensive care unit did not exceed one day for any patient.

The mean dynamic blood pressure in the patients before surgery was 93.4 ± 1.8 mm Hg. The blood pressure increased on days 2–4 after surgery in 83.3% (n = 30) patients post-nephrectomy and in 13.6% (n = 3) patients

who underwent kidney resection. The mean dynamic blood pressure in these patients was 105.6 ± 2.4 mm Hg. From day 3–4, blood pressure stabilized, with an average dynamic value of 108.4 ± 2.4 mm Hg ($p < 0.05$ compared to the baseline values).

Ultrasounds performed on the days 4–5 after the surgery showed an increase in the size of the solitary kidney remaining after nephrectomy by an average of 4%, from 126.1 ± 1.4 cm^3 to 131.2 ± 2.1 cm^3, respectively ($p < 0.05$). After resection of the kidney, there were no significant signs of changes in the size of the kidneys.

The median preoperative GFR was 102.4 ± 9.4 mL/(min·1.73 m^2) and was similar in both groups ($p > 0.05$). After surgery, a decrease in GFR was detected in 34 (58.6%, $p < 0.05$) patients: after nephrectomy ($n = 28$) up to 73.4 ± 8.2 mL/(min·1.73 m^2), and after kidney resection ($n = 6$) up to 98.2 ± 3.4 ml/(min·1.73 m^2). A pronounced decrease in GFR [(<30 mL /(min·1.73 m^2)] was recorded in 3 patients ($p < 0.05$) after nephrectomy, corresponding to stage IV chronic kidney disease according to the KDOQI classification (Kidney Disease Outcomes Quality Initiative, 2002). There was an increase in urea and creatinine levels by 8% ($p < 0.05$): hypercreatininemia (more than 177 mmol/L) in 25% ($n = 9$) patients after nephrectomy and in 4.5% ($n = 1$) after kidney resections, gradually returning to normal by days 10–15.

Doppler ultrasonography of the vessels within the solitary kidney in patients after RNE showed a significant increase in linear blood flow up to 1.15 cm/s ($p > 0.05$) in 83.3% of cases ($n = 30$). On assessing the resistance index, its significant increase in the main trunk of the renal artery up to 0.72 ± 0.02 was noted in 16.1% of patients compared to the values in the control group which were 0.62 ± 0.02 ($p < 0.05$), with the blood flow remaining unchanged in the segmental arteries as 0.69 ± 0.01 (in the control group 0.61 ± 0.01, $p > 0.1$) and in the arcuate arteries of 0.66 ± 0.04 (in the control group 0.6 ± 0.03, $p > 0.1$). The pulsation indices in the main trunk of the renal artery were similar between patients with a solitary kidney after nephrectomy and in the control group (0.64 ± 0.07 and 0.68 ± 0.08, respectively, $p > 0.1$), meanwhile the value of this indicator in patients after RNE was significantly lower in segmental arteries (0.54 ± 0.08 and 0.88 ± 0.08, respectively, $p < 0.05$) and arcuate arteries (0.64 ± 0.06 and 0.89 ± 0.06, respectively, $p < 0.05$) compared with the control group.

The resistance and pulsation indices reflect the microvasculature state to a greater extent, namely the tone of arterioles and capillaries. Moreover, the state of the vessels is indicated by the pulsation index. A decrease in the value of this indicator is noted in cases of arteriovenous shunting or in severe peripheral vasodilation. In our patients after RNE, an increase in the resistance index in the main trunk of the renal artery is most likely associated with a vasospastic reaction of the renal vessels. In the segmental and arcuate arteries, both indices tend to decrease, especially the pulsation index, apparently due to peripheral venous edema with an increase in peripheral resistance. The results of the Doppler ultrasound of the renal vessels were confirmed by the data obtained during the biomicroscopy of the bulbar conjunctiva. It was noted that in the majority of patients after RNE (83.3%) and in 13.6% after resection of the kidney, the arterioles in the microcirculation system were narrowed, the venules were significantly dilated and convoluted, the venular and capillary blood flow sharply decreased, erythrocytes underwent a distinct aggregation in the capillaries, which reflects a disorder of microcirculation in organs and tissues.

The state of microcirculation is largely determined by the rheological properties of blood. The table presents the results of a study of the content of fibrinogen and soluble fibrin-monomer complex (SFMC) in RCC patients before and at various times after surgery, as well as in the control group. From the table, the levels of fibrinogen and SFMC in RCC patients were significantly higher than in the control group ($p < 0.05$).

Fibrinogen is known to be an acute phase protein in any inflammatory, specific, and nonspecific processes. This can be due to its steadily increased level in response to the presence of an oncological process. Thrombin levels increase at the beginning of the postoperative period as well as the level of SFMC. We have established that its value in the perioperative period was subject to significant fluctuations, characterizing the greatest "thrombogenic alertness" in the early postoperative period. With the use of low-molecular-weight heparins in the postoperative period, there is a more pronounced decrease in the SFMC index, compared with the control value up to 10 days (Table 1).

During the surgical treatment of RCC patients after nephrectomy, in the tissue of a solitary kidney, parenchymal and interstitial edema occur with the development of compensatory functional overload of the kidney and the formation of capillarostasis, vascular (circulatory) stress, tissue hypoxia, as well as a number of metabolic disorders due to endocytosis and exotoxicosis [14–16]. The subsequent increase in renal plasma flow and pressure in the renal vessels is accompanied by an increase in vascular permeability, the development of the so-called pathophysiological edema of the renal cortex with an increase in the resistance index in the main trunk. Thus, in our opinion, compensatory and adaptive reactions are engaged in the drainage and detoxification of tissues exposed to stress (including circulatory stress) as a result of nephrectomy [15].

Table. Fibrinogen and Soluble Fibrin Monomer Complex indices in patients with RCC and in the control group

Таблица. Показатели фибриногена и растворимого фибрин-мономерного комплекса у больных почечно-клеточным раком и в контрольной группе

Patient groups	Fibrinogen, g/L	SFMC, 10^{-2} g/L
RCC patients (n = 58)		
• before surgery	5.2 ± 0.3*	17.9 ± 1.2*
• on the day of surgery	5.7 ± 0.9*	22.3 ± 0.6*†
• day 1 after surgery	5.7 ± 0.5*	23.0 ± 0.5*†
• day 7 after surgery	5.2 ± 0.8*	20.2 ± 0.8*†
• day 10 after surgery	4.9 ± 0.3*	17.0 ± 0.5
• Control group (n = 16)	2.8 ± 0.4	3.5 ± 0.3

* The difference from the value in the control group is statistically significant ($p < 0.05$); †the difference from the value before surgery is statistically significant ($p < 0.05$).

In experiments on laboratory animals (Wistar rats) [17], it was revealed that the adrenaline levels on day 7 after nephrectomy decreased by 78% ($p > 0.05$), and after kidney resection by 38% ($p > 0.05$), whereas on the day 16 of the experiment, in comparison with the day 7, in the group of rats after resection, there was a 13% increase in the level of adrenaline ($p > 0.05$), and after nephrectomy, it increased by a factor of 2.3 ($p > 0.001$). These results indicate a more economical and efficient work of the neuroendocrine system, microcirculation vessels, lymphatic drainage function and metabolism in general, in organs and tissues after kidney resection as compared to nephrectomy.

Renal pathology is often accompanied by arterial hypertension, which is also an important factor in kidney damage in itself. During prolonged arterial hypertension, tissue remodeling is noted, accompanied by structural and functional restructuring of the organ. Nephrectomy, apparently, leads to a "restart" of the work of the solitary kidney due to the reduced amount of the functioning renal parenchyma [18]. Vascular-parenchymal disorders lead to venous-lymphatic edema of the interstitium, the development of vicarious hypertrophy, tissue ischemia and compensatory renoparenchymal nephrogenic arterial hypertension. According to the mosaic theory of arterial hypertension, an increase in blood pressure represents a compensatory response to a decrease in tissue perfusion due to the influence of nervous and humoral factors: cardiac output volume, elasticity, diameter and lumen of blood vessels, and blood viscosity. Thus, nephrectomy forms a pathologically vicious circle, contributing to the development and further progression of kidney and heart failure.

CONCLUSIONS

The solitary kidney in RCC patients after nephrectomy undergoes functional and pathophysiological restructuring, accompanied by vicarious organ hypertrophy, increased renal blood flow, and an increase in the resistance index at the level of the great vessel. Hemorheological indices are impaired in the direction of hypercoagulation (hyperfibrinogenemia and an increase in the level of SFMC). Impairment of microcirculation is confirmed by the data of biomicroscopy of the bulbar conjunctiva (slowing of capillary blood flow, stasis of blood corpuscles). This indicates the formation of circulatory stress, which contributes to the development of systemic arterial hypertension.

In our opinion, organ-preserving techniques, namely kidney resection can be considered the method of choice in the treatment of kidney cancer as it enables not only to perform effective postoperative rehabilitation, but also generate the most favorable prognosis in the treatment of patients with kidney cancer, considering the preservation of the functional reserve not only of the contralateral kidney, but also resected one. Rescue nephrectomy (due to medical necessity) in conditions of a sharply increased function of a solitary kidney requires long-term complex medical and socio-economic rehabilitation in the future.

ADDITIONAL INFORMATION

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